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Sex Differences in Drug-Related Stress-System Changes: Implications for Treatment in Substance-Abusing Women

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Abstract

Extensive research indicates that chronic substance abuse disrupts stress and reward systems of the brain. Gender variation within these stress-system alterations, including the impact of sex hormones on these changes, may influence sex-specific differences in both the development of, and recovery from, dependency. As such, gender variations in stress-system function may also provide a viable explanation for why women are markedly more vulnerable than men to the negative consequences of drug use. This article therefore initially reviews studies that have examined gender differences in emotional and biophysiological changes to the stress and reward system following the acute administration of drugs, including cocaine, alcohol, and nicotine. The article then reviews studies that have examined gender differences in response to various types of stress in both healthy and drug-abusing populations. Studies examining the impact of sex hormones on these gender-related responses are also reported. The implications of these sex-specific variations in stress and reward system function are discussed in terms of both comorbid psychopathology and treatment outcome.

Keywords

gender; stress; substance abuse

INTRODUCTION

Drug and alcohol dependence is now viewed as one of the most common and preventable health care problems in the United States. Although rates of substance abuse are higher in men than women,¹ global studies have indicated that in the last decade, due to changing socioeconomic factors, women have become increasingly more abusive of drugs and alcohol. Hazardous, heavy episodic drinking is increasing in younger women,² and a recent survey indicated that young adult females are consuming similar amounts of drugs and alcohol as men.³ This problem may be exacerbated by the fact that distinct gender differences, which increase addiction vulnerability for women, are observed at every phase in the drug reinforcement process, including acquisition, maintenance, and outcome.⁴

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Preclinical models that have been used to mimic the loss of control of drinking and substance use in humans have highlighted robust variation, by sex, in factors affecting both the development of, and recovery from, dependency. For example, female rats have been shown to acquire cocaine, methamphetamine, heroin, alcohol, and nicotine self-administration more rapidly than male rats.^{5–8} They also show greater escalation and dysregulation in pattern and quantity of drug intake during extended-access regimens.^{9,10} Likewise, in the human literature, females report markedly different subjective effects of both psychostimulants and alcohol,^{11, 12} and they progress to drug dependence more rapidly than men,¹³ through more addictive routes.^{14,15} Extensive research shows that the negative consequences of drinking and drug use in females appear accelerated or “telescoped,” particularly in relation to co-occurring psychopathology such as depression, phobias, and panic and eating disorders.^{16,17}

Many interacting psychosocial and biological processes may be associated with an increased vulnerability to compulsive drug or alcohol seeking in women compared to men. The current article focuses on reviewing studies that have assessed the influence of gender and gonadal hormones on drug-related changes to stress-system function and on how these emotional and biophysiological alterations may affect co-occurring psychopathology, as well as relapse and treatment outcome, in substance-abusing women.

Association Between Stress and Substance Use

Many well-established preclinical and human models of addiction propose that chronic stress can play an integral part in the motivation to abuse drugs and to maintain alcohol abuse in addicts,^{18–21} and that it can provide an impetus for increased alcohol consumption in social drinkers.²²

In laboratory animals, experimental manipulations using various stress paradigms such as tail pinch, food deprivation, and electric foot-shock have been shown to increase the acquisition and reinstatement of stimulants, opiates, and alcohol.^{23–25} Well-established human models of addiction such as stress-coping²⁶ and relapse-prevention²⁷ models also present addiction as either a maladaptive coping response to life stressors or as a biopsychosocial risk factor for individuals with poor coping strategies, whereas the tension-reduction²⁸ and self-medication²⁹ models emphasize the basic need to boost positive affect via either positive (mood enhancement) or negative (relief from stress) reinforcement processes.²¹ Furthermore, many treatment and laboratory studies have documented that stress- and negative mood-induced craving are robust predictors of treatment outcome and relapse in alcohol-dependent^{30–33} and cocaine-dependent^{34,35} individuals.

Drug-Related Changes in Stress-System Engagement and Relapse

In view of the above results, both animal and human research has shown that drug-related changes to the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic adrenal medullary system (SAM), and mesolimbic dopamine (DA) stress and reward systems may underlie the pathophysiology of drug addiction.^{36–38} For example, extensive literature has highlighted substantial interacting and overlapping neural circuitry involved in both stress and putative reward circuits.^{39,40} Research findings indicate that “engagement” of the stress system may serve to “prime” the brain’s reward circuits²¹ by modifying reward-related behavior through stimulation of mesencephalic dopaminergic transmission.⁴¹ Moreover, according to the recent allostatic model of addiction, this sustained increase in the secretion of DA may reflect a compromise in homeostasis and result in a decrease in the function of reward neurocircuitry and an increase in sensitivity of the stress-related systems,⁴² potentiating both the positive and negative reinforcing effects of psychostimulants, opioids, and alcohol.

Support for this stress and reward-system dysregulation has been reflected in preclinical studies showing that acute administration of both psychostimulants and alcohol mediates DA transmission, HPA function, and glucocorticoid release.^{43–47} Furthermore, in humans, acute and chronic substance abuse and withdrawal are associated with changes in basal cortisol and ACTH tone,^{48–50} as well as with dysregulated HPA/SAM system and cardiovascular response to both psychosocial and physiological stressors.^{51–55}

These drug-related changes to brain stress and reward systems have been associated with enhanced emotional and behavioral sensitivity to stress during protracted withdrawal—including increased reports of irritability, restlessness, depressed mood, anxiety, and high cravings.^{21,56,57} Studies from our own laboratory have shown that early protracted abstinence from both drug and alcohol addiction is characterized as a craving “state” comprising enhanced emotional and behavioral distress, along with robust changes in physiological and neuroendocrine markers.^{54,58–60} Most importantly, these alterations in stress-system emotional and biophysiological markers associated with influencing the transition from controlled drug seeking to addiction^{61,62} are gender specific.

Prior research has assessed gender variation in emotional, physiological, and autonomic stress-system adaptations in order to better understand important differences in the stress-related craving state and compulsive drug seeking. In order to assess these findings on gender variation, we have reviewed the literature in four distinct sections reflecting the different methodological paradigms employed to compare stress-system adaptations in male and female healthy volunteers and substance abusers: (1) gender differences in stress-system changes following acute drug administration; (2) the impact of sex hormones on stress-system function following acute drug administration; (3) the impact of sex hormones on stress-system function following exposure to stress; and (4) gender differences in stress-system changes following exposure to stress.

In all four sections the literature was identified using Medline search terms “gender differences” and “sex differences” for each drug type (viz., cocaine, alcohol, d-amphetamine, and nicotine). In addition, the search terms “acute,” “administration,” “menstrual cycle,” and “stress” were selectively included for the relevant sections. The review was restricted to studies of human adult populations published in English between 1970 and 2008. Studies identified through the primary searches were also included.

GENDER DIFFERENCES IN STRESS-SYSTEM CHANGES FOLLOWING ACUTE DRUG ADMINISTRATION (TABLE 1)

As there exists an overlap in neural systems between stress response and the acute effects of many psychoactive drugs, gender-related differences in either may help identify some of the sex-specific mechanisms underlying stress-induced drug seeking. This cross-sensitization between stress response and the acute effects of drugs is related to the fact that drugs such as cocaine, alcohol, d-amphetamine, and nicotine are known to stimulate the HPA-axis stress systems in animal and humans.^{86–88} Moreover, enhanced stress-system sensitivity and increased positive, subjective-reinforcing effects in acute drug response have been seen as markers for increased risk of problematic drug use and abuse potential.^{20,89,90}

Preclinical data have indicated that female rats demonstrate a more sensitized biophysiological and behavioral response to acute drug administration compared to male rats. They show greater HPA-axis response to alcohol⁹¹ and greater locomotor activity following cocaine exposure compared to male rats.⁹² Female rats also show significantly increased locomotor activity, orofacial activity, and ACTH and cortisol levels, as well as a decrease in D3 dopamine transporters, in response to nicotine compared to male rats.^{93–95}

In the human literature, findings are far more complex and largely dependent on drug, dosing pattern, route of administration, and subject population. Gender differences in stress-system adaptations to the acute administration of drugs have typically been assessed either by comparing pharmacokinetic, physiological, and subjective effects of drugs in men versus women,^{65,66} or by examining the effects of sex hormones on these drug-reinforcing stress-system alterations.^{82,83} In view of the complex interactions between hormonal status and stress, studies have either assessed the acute effects of a drug at various stages of the menstrual cycle (MC) in female subjects^{77,78} or examined the effects of exogenous sex hormone levels on acute drug exposure in both men and women.^{84,85}

In relation to psychoactive stimulants, studies assessing the acute effects of cocaine on subjective and physiological response in men and women have typically been conducted in subjects who either are cocaine dependent (CD) or report a history of regular cocaine use. Although these studies have all employed different paradigms with regard to design, route of administration, and cocaine dose (Table 1), three of the four cocaine-administration studies reviewed here have shown females to demonstrate increased subjective sensitivity to physiological changes following cocaine administration. Kosten and colleagues¹¹ collated data from the placebo phases of four different studies in 23 CD males and 11 CD females. Findings indicated that although peak plasma cocaine levels, heart rate, and blood pressure were similar across gender following intranasal cocaine administration, females showed greater self-reported “nervous” responses compared to males. Similarly, after administering cocaine orally to 27 men and 8 females, Singha and colleagues⁶⁶ documented increased reports of “bad drug effects” and higher ratings of “anxious/nervous” in female CD subjects compared to men, alongside lower systolic blood pressure. Higher ratings of “feeling good” were also reported in comorbid CD and alcohol-dependent (AD) women compared to men, following persistent (4×1 mg/kg) intranasal cocaine administration.¹²

Conversely, one study by Evans and colleagues⁶⁵ showed prolonged physiological effects of repeated smoked cocaine, as well as higher plasma concentrations, in females with a history of cocaine use, but no gender differences in ratings on subjective emotional visual-analog scores. Although the higher peak plasma levels of cocaine were attributed to the women effectively receiving a higher dose than the men due to weight differential,⁶⁵ the lack of enhanced sensitivity observed in the CD women may have been related to variations in drug-use severity (subjects reported a cocaine history rather than met DSM-IV dependence criteria) and to differences in route of administration.

In addition to studies documenting the subjective reinforcing effects of cocaine in dependent populations, a study by Lukas and colleagues⁷² demonstrated that healthy, non-drug-using women are more sensitive than healthy men to stress-system cardiovascular adaptations associated with intranasal cocaine. After giving a single intranasal dose of 0.9 mg/kg cocaine to 7 male and 7 female healthy volunteers, women demonstrated significantly lower plasma cocaine levels than men, though no gender variation was observed in relation to peak heart rate or response on subjective visual-analog scales.

These findings are consistent with gender differences in stress-system sensitivity following nicotine administration in healthy smokers. Two studies administering varying levels of nicotine to men and women who were regular smokers and social drinkers indicated that females were more sensitized to both the cardiovascular and subjective effects of nicotine. After administering 0.014 and 0.028 mg/kg of nicotine to a group of healthy men and women, Netter and colleagues⁶³ showed that although men had significantly higher serum nicotine levels compared to women, women demonstrated significantly higher heart rate and blood pressure at the lower, 0.014 mg/kg dose. Similarly, Acheson and colleagues⁷⁰ showed that following administration of 0, 7, and 14 mg nicotine transdermally in males and females,

females reported significantly higher positive mood compared to males following both placebo and the lower, 7 mg dose.

These findings highlight both reward system changes and a potentially sensitized response to stress in cocaine- and nicotine-dependent females. However, in marked contrast to these results, data from studies that have administered d-amphetamine and alcohol to groups of healthy men and women show different findings. In studies where a single dose of d-amphetamine has been given to groups of healthy male and female volunteers, greater drug sensitivity has been reported in males.^{68,69,71} Gabbay and colleagues⁶⁸ found that healthy males reported significantly higher ratings of anxiety following a 10 mg/kg dose of d-amphetamine compared to healthy females. In addition, a later study by the same group indicated that males with a positive family history of alcohol abuse were significantly more sensitive to the stimulant effects of amphetamine compared to males who had no family history of alcohol abuse.⁶⁹ Moreover, this difference in sensitivity was not observed in the females.⁶⁹ A more recent study by Vansickle and colleagues⁷¹ also found that healthy males reported feeling more “high” than healthy females, despite demonstrating significantly lower diastolic blood pressure.

In relation to alcohol administration, findings are similar. Perkins and colleagues⁶⁴ found that in males but not females, alcohol significantly reduced reported vigor and arousal compared to baseline. In addition, a study assessing the acute effects of a single dose of alcohol (adjusted for gender variations in body weight) reported no significant gender differences on all subjective scales of the Subjective High Assessment Scale.⁶⁷ It is possible that some of the inconsistencies pertaining to these gender variations in subjective and physiological stress-system sensitivity may, among other factors, be related to both drug and subject sample. Whereas studies examining the effects of cocaine were largely conducted in dependent samples,^{11,12,65,66} studies assessing the effects of amphetamine employed either healthy volunteers⁶⁸ or healthy “at risk” populations.⁶⁹ Moreover, both studies examining the sex-specific effects of alcohol were conducted in samples of nonaddicted social drinkers.^{64,67}

These differences in group dependency status may account for the disparity observed in gender-related stress-system sensitivity. For example, the alcohol literature indicates that gender differences in stress-system engagement prior to alcohol exposure may vary in addicts compared with social drinkers. Findings from social drinkers indicate, for example, that the incentive value of alcohol may be less sensitized by negative mood and stress in female social drinkers than in male social drinkers.^{96,97} By contrast, findings from alcoholics show that females demonstrate greater alcohol cue reactivity following negative mood induction compared to males.⁹⁸ Although these studies represent different paradigms, they do reflect robust gender dissociations between nonaddicted and addicted populations in relation to stress-system function, albeit in response to stress rather than acute drug administration.

THE IMPACT OF SEX HORMONES ON STRESS-SYSTEM FUNCTION FOLLOWING ACUTE DRUG ADMINISTRATION

Complex interactions between the HPA and hypothalamic-pituitary-gonadal axes may also have a salient impact on gender variation in relation to stress-system function following drug intake. For example, in animals, estradiol has been shown to have an excitatory effect on the HPA axis,⁹⁹ and in humans, progesterone and estrogen both show modulating effects on the HPA axis.^{100,101} As such, sex hormones may influence stress-system engagement following acute drug administration and subsequently influence behavioral response to drugs,^{20,102} especially with regard to craving and relapse vulnerability in women. In order to examine this hypothesis, several studies have assessed the influence of the MC on acute response to drugs in groups of both healthy and substance-abusing men and women.

The majority of the research to date has indicated that MC phase appears to have a significant impact on both the subjective and pharmacokinetic effects of stimulant drugs, including cocaine, amphetamine, and methamphetamine. Drugs such as alcohol, nicotine, marijuana, and benzodiazepines have been shown to have a limited effect on the MC in both animals and humans,¹⁰³ though reproductive problems such as early menopause, amenorrhea, and luteal phase dysfunction have been associated with chronic misuse of these drugs.^{104,105} As such, a more precise endocrine profile of MC disruption in nonstimulant drugs may still need to be elucidated.

An initial study by Justice and De Wit⁷⁷ reported that the positive subjective effects of d-amphetamine such as “high,” “euphoria,” and “like drug” were potentiated in 16 healthy females during the follicular (low estrogen and low progesterone), compared to the mid-luteal (high progesterone), phase of their MC. Similarly, White and colleagues⁷⁵ found that 13 normally cycling healthy women reported greater amphetamine-induced subjective stimulation in their follicular, compared to luteal, MC phase. In the same study 7 healthy males reported significantly greater subjective stimulation than females who were in the luteal, but not those who were in the follicular, phase.⁷⁵ Research comparing 19 healthy women in both the early (low estradiol) and late (high estradiol) follicular phases of their MC found that most of the subjective effects of d-amphetamine were unaffected by the estradiol-related changes during the follicular phase, suggesting less of a role for estradiol in potentiating the effects of amphetamines and a potentially greater role for progesterone in masking the acute effects.^{80,106}

Several studies support this last hypothesis. First, exogenous administration of estradiol was shown not to enhance either the subjective or pharmacokinetic effects of d-amphetamine in 20 healthy, normally cycling women⁸¹ except for an increase in subjective ratings of “pleasant stimulation” and decrease in ratings of “want more.” Second, exogenous progesterone was shown to have an attenuating effect on the subjective^{82,85} and physiological⁸⁴ effects of smoked cocaine in follicular phase CD women. Similar subjective effects of cocaine (following smoked cocaine) were also potentiated in the follicular, compared to mid-luteal, MC phase of 11 women with a history of regular cocaine use, although ratings were dependent upon dose.⁷⁸ Progesterone may attenuate the subjective effects of cocaine and amphetamine in both CD and healthy women, respectively, though the precise, sex-specific mechanisms underlying this process remain ambiguous. While Sofuoglu and colleagues⁸⁴ reported that feelings of “high,” “feeling the effects” of cocaine, and diastolic blood pressure were reduced in both women and men, Evans and Foltin⁸⁵ reported attenuated effects of cocaine in women only.

A subsequent study comparing the effects of cocaine in 23 CD men compared to 21 CD women in both the follicular and luteal MC phases demonstrated that the subjective effects of drugs, such as “feeling high,” were potentiated in women during the follicular phase, though comparable to men.⁷⁴ Conversely, women in the high-progesterone, luteal MC phase were shown to report attenuated effects compared to men.

Notably, the above studies assessed the subjective and physiological reinforcing effects of *smoked* cocaine. In three studies examining the effects of intranasal^{76,79} and intravenous⁷³ cocaine, no MC influence was observed in either CD subjects or healthy volunteers, suggesting that the impact of gender and MC phase on acute stimulant administration may vary as a function of route of administration.⁷⁶

In summary, these studies broadly indicate that females may have a sensitized subjective response to the acute administration of cocaine. Moreover, high progesterone levels during the mid-luteal phase may serve to “mask” some of the positive subjective effects of cocaine in CD women.

THE IMPACT OF SEX HORMONES ON STRESS-SYSTEM FUNCTION FOLLOWING EXPOSURE TO STRESS

Studies in our laboratory have further investigated the impact of sex hormones on stress-system function during a period of high stress and also following personalized stress-related imagery exposure. In an initial study, we assessed daily levels of salivary cortisol, estradiol, and progesterone at waking in a group of 12 CD women following admission to inpatient treatment, comparing them to a group of 10 healthy control women, across one complete 28-day MC.⁵⁵ Weekly measures of negative emotion were also collected in all women, and cocaine-craving measures were collected in the CD women only. Findings indicated that levels of waking cortisol and progesterone, but not estradiol, were significantly higher in the CD women compared to controls. Significantly lower E2/P ratios were also observed in the CD women, largely as a result of high waking levels of progesterone. CD women also reported significantly higher overall negative emotion. Although ratings of cocaine craving did not change in CD women as a function of MC phase, craving did correlate positively with negative mood in the follicular and luteal phases. Increased levels of progesterone in early-abstinent CD females may represent compensatory adaptations to an enhanced HPA-driven distressed state and is consistent with the possibility that progesterone may reduce the positive effects of d-amphetamine and cocaine.^{82,84,85}

In a follow-up study to assess the effects of MC phase more systematically on stress and cue-related cocaine craving, we compared the reactions of three groups of CD women to stress, drug-cue, and neutral imagery exposure using our standard procedures.¹⁰⁷ The groups included five women with high progesterone levels to match the mid-luteal MC phase ($P = 11.8$ ng/ml, $SD = 2.9$; $E = 69.1$ pg/ml, $SD = 43.2$); five women with high estradiol levels and low progesterone levels to match the late follicular MC phase ($P = 0.44$ ng/ml, $SD = .21$; $E = 112.46$ pg/ml, $SD = 118.3$); and nine women with moderate levels of estradiol and progesterone ($P = 2.7$ ng/ml, $SD = 2.85$; $E = 60.19$ pg/ml, $SD = 66.9$) corresponding to the early luteal MC phase.

Findings indicated that the CD women with high progesterone levels reported significantly lower stress, cue-induced cocaine craving, and cue-induced anxiety, as well as had decreased cue-induced blood pressure, compared to the women with high estradiol levels and low progesterone levels. These findings also corroborate previous human studies that show intramuscular progesterone treatment to significantly attenuate epinephrine and heart rate responses to mental stress.¹⁰⁸ Most importantly, findings confirm the acute-administration studies and demonstrate that increased progesterone levels are able to regulate selective aspects of the stress- and cue-induced craving state in mid-luteal CD women.

GENDER DIFFERENCES IN STRESS-SYSTEM CHANGES FOLLOWING EXPOSURE TO STRESS (TABLE 2)

To date, preclinical studies have been fairly consistent in demonstrating a more extensive response to various stress paradigms in female, compared to male, laboratory rats. Female rats show significantly greater corticosterone and ACTH levels than male rats, both at baseline¹³² and in response to stressors such as footshock and restraint stress.^{43,133,134} Female rats also show longer activation of the HPA axis¹³⁵ and demonstrate greater behavioral sensitivity (locomotor activity, vocalizations, and flinching) to stressors compared to male rats.¹³⁶ In relation to catecholaminergic markers, norepinephrine response to controlled, compared with uncontrolled, stress is also greater in female rats, and footshock initiates greater neural activity in monoaminergic brain regions of female, versus male, rats.^{137,138} Studies that have examined the effects of both stress and drug administration on behavioral sensitivity have shown maternal separation to facilitate behavioral sensitization to alcohol in female, but not

male, rats.¹³⁹ Similarly, following restraint stress and nicotine exposure, female rats show increases in horizontal activity and decreases in feeding and body weight to a greater extent than male rats.^{94,140}

In humans the broader picture is far more complex. In general, gender-specific emotional and biophysiological responsivity to stress has been shown to vary in relation to both the nature of the substance being abused and the type of stressor. In drug abusers this responsivity may be associated with drug-related neuroadaptations to the stress and sex hormonal systems.

The first human studies in healthy populations examining variations in response to stress between men and women were conducted by Marianne Frankenhaeuser's group in Stockholm during the 1970s. A series of refined studies using student samples assessed gender differences in response to examination and cognitive stress, and indicated fairly consistently that women demonstrated a reduced epinephrine response compared to men,^{109,110} as well as lower cortisol and heart rate.¹¹¹ In one study, 19 student males were compared to 30 student females in response to examination stress. Findings showed a reduced catecholamine response to examination stress in females, along with lower ratings of "success and confidence."¹¹⁰ These findings were pioneering in showing that females may be more emotionally sensitive than males to catecholamine response and also that females may be less affected by achievement challenges. The latter is consistent with a later study by Stroud and colleagues¹²⁵ that compared self-reported affect and salivary cortisol responses in 24 healthy males and 26 healthy females randomly assigned to either an achievement stress (a mathematical and a verbal challenge) or social rejection situation (two social interaction challenges). Although no significant gender variation was reported in mood ratings, men showed significantly greater cortisol responses to the achievement challenges, whereas women showed greater cortisol responses to the social rejection.

Despite these potential interactions between gender and stress type, findings from young healthy population samples have typically shown that males demonstrate higher heart rate,^{115,117,123,128} blood pressure response,^{113,117,122,123} and HPA-axis sensitivity^{116,119,121} across a range of laboratory challenge studies compared to healthy females. These challenges have included public speaking, mental arithmetic,^{116,119,121} pain,¹¹⁹ cognitive challenge,¹²⁴ harassment,¹²² and mirror-drawing tasks.¹¹⁷ Exceptions have included studies employing physical exercise as a stressor, where no gender variations have been documented.^{116,141} Furthermore, although consistency in response to psychological stress has been shown in some studies employing elderly populations,^{119,124,126} others have highlighted sex-specific differences. A reanalysis of five independent studies from the same laboratory populations indicated increased plasma, but not salivary, cortisol levels in elderly women compared to elderly men and a suggestion that the heightened HPA sensitivity documented in younger adult males may decrease with age.¹⁴²

Notably, despite young adult males displaying increased physiological, stress-related activity compared to females, females have tended to report significantly higher levels of distress. This finding is consistent with data from several of the studies mentioned previously in relation to stress-system changes following the acute administration of psychoactive drugs. In all cases, a more sensitized emotional response to biophysiological stress-system activity following either stress or acute drug administration may predispose women to specific risk factors for addictive disorders. Recently, several studies have assessed stress and drug-cue responses within addicted populations and have highlighted important gender variations in autonomic and affective functioning.

Consistent with research on healthy volunteers, studies comparing male and female cocaine abusers have indicated that CD males may have a significantly higher HPA-axis drive than CD

women. In a study conducted in our laboratory, we found that 25 CD women demonstrated significantly lower ACTH, cortisol, and blood pressure drive compared to 25 CD men, despite similar ratings of subjective anxiety following exposure to personalized, individually calibrated stress, drug-cue, and neutral imagery.¹²⁹

One of the limitations of the above study was the exclusion of a healthy control group, making it difficult to assess whether CD males demonstrated a hyper-HPA response compared to healthy males, or whether CD females demonstrated a hypo-response compared to healthy females. In a subsequent study using an identical paradigm, however, we examined the impact of both gender and drug group on emotional and cardiovascular response to stress imagery in 40 CD individuals and 40 social drinkers.⁶⁰ Findings indicated that the CD males demonstrated an enhanced change from baseline heart rate response to stress compared to both the social-drinking males and CD females. Consistent with the emotional sensitivity to stress-system engagement shown in healthy females following stress and acute administration of cocaine, findings indicated that females in general (36 total [CD or social drinkers]) reported significantly higher levels of anxiety and sadness following exposure to stress compared to males (44 total [same groups]).

In relation to gender variation in adrenal sensitivity, extended analyses from Fox and colleagues¹²⁹ found that ACTH and cortisol were correlated in the 25 CD males, but not in CD females, following both stress and drug cue. This low ACTH and cortisol conformity may also highlight a failure of the adrenal cortex to respond normally to ACTH stimulation when the HPA system is challenged under psychologically stressful conditions. Previous research has interpreted a lack of synchrony between ACTH and cortisol as reflecting a potential disturbance in the regulation of cortisol secretion and disruption in hormonal release patterns—which could increase vulnerability to neuroendocrine dysfunction.^{143,144} Further alterations in adrenal responsiveness were evident in that CD females did not demonstrate the hypersensitivity to ACTH in relation to the production of glucocorticoids typically observed in normal, healthy females.¹⁴⁵ Again, although a healthy control group was not included in this study, previous studies using healthy volunteers have tended to show higher levels of basal ACTH, but not cortisol, in males,^{146–148} suggesting a different set-point to cortisol feedback in healthy females. This sensitivity was not demonstrated in CD women.¹²⁹

In addition, several studies have reported similar gender-specific changes in both emotional and behavioral set-point following exposure to stress in alcohol-dependent females. Employing an identical personalized imagery paradigm to that used with CD subjects, we compared a group of AD and social-drinking males and females across three imagery conditions (stress, alcohol cue, and neutral/relaxing) and assessed emotional and behavioral response at baseline, immediately following imagery exposure, and at various time-points. Similar to CD females, 21 early-abstinent AD females reported significantly higher ratings of stress-induced sadness, anxiety, anger, fear, and behavioral arousal compared to 21 AD males as well as to 21 social-drinking males and females.¹⁴⁹

In relation to HPA-axis markers, a recent study by Brady and colleagues³³ demonstrated gender-related basal and response differences to the cold pressor task in three groups of individuals (AD, posttraumatic stress syndrome [PTSD], and comorbid AD and PTSD). Forty-five females showed significantly lower levels of ACTH compared to 47 males (across all three groups), and 12 females with either AD or PTSD showed greater ACTH blunting following stress exposure compared to 16 males meeting the same diagnostic criteria.

In addition, findings from a recent study by Back and colleagues¹³⁰ indicated that, similar to AD women, stress-induced HPA-axis response was more reduced in female than in male smokers. The study involved male and female smokers and nonsmokers being exposed to both

the Trier Social Stress Test¹¹⁸ and a corticotrophin-releasing hormone challenge. Female smokers demonstrated significantly lower basal cortisol levels compared to female non-smokers, as well as a blunted cortisol response to both the physiological and psychosocial stressor compared to female nonsmokers. Importantly, these variations in smoking-related adaptations were not observed between the male smokers and nonsmokers, and may have some role in explaining why women have markedly greater difficulty than men in quitting smoking.^{150–152}

THE IMPLICATIONS OF GENDER DIFFERENCES IN STRESS-SYSTEM CHANGES

Although methodological complications regarding drug type, stressor type, and subject sample make it difficult to formulate detailed conclusions concerning gender variation in stress-system changes, there are some broad consistencies. First, an enhanced emotional sensitivity to biophysiological stress-system changes is typically observed in female substance abusers compared to males, particularly following the acute administration of cocaine and nicotine. Inconsistencies following the administration of amphetamine may reflect the character of the samples, which included nonaddicted subjects. Second, following exposure to both stress and drug cue, cocaine- and alcohol-dependent females typically report an enhanced emotional response relative to their biophysiological stress-system arousal. Third, a dysregulated HPA-axis response is documented in both CD and AD females. In CD females, a low conformity in stress- and drug cue-related ACTH and cortisol response, as well as potential alterations in cortisol feedback, may be indicative of adrenal cortex failure to respond normally to ACTH stimulation under challenging situations. Similarly, a blunted cortisol response to stress in alcohol- and nicotine-dependent women may represent an important risk factor for relapse. HPA-axis hyporeactivity to social stress, alcoholcue exposure, and alcohol consumption has been associated with greater craving and with a return to early drinking in alcoholics,^{153–155} and has also been deemed a risk marker for the development of substance use disorders in individuals with a positive family history for alcoholism.¹⁵⁶ Fourth, MC changes marked by fluctuations in sex hormones can influence these stress-system adaptations in substance-abusing women.

Findings relating to enhanced emotional sensitivity in substance-abusing women may be largely reflective of trends in the general population,^{17,157,158} as healthy and socially drinking females also report increased stress-related anxiety and negative affect following stress.^{122, 131} In drug-abusing women, enhanced emotional sensitivity to a stress-related craving state, along with differences in adrenal response, may increase risk of relapse vulnerability and also highlight dissociations in risk for comorbid disorders between men and women.

Increased anxiety, anger, fear, and sadness reported by AD females¹⁵⁰ have been significantly associated with stress-induced alcohol craving in alcoholics,^{58,59} and increased stress-related anxiety and sadness have been significantly associated with stress-related cocaine craving in cocaine abusers.⁶⁰ Furthermore, meta-analyses of international longitudinal surveys have shown that emotionally driven, internalizing disorders such as depression are predictive of drinking in women but not in men.¹⁵⁹ Similarly, affective problems such as low self-esteem, guilt,¹⁶⁰ stigmatization,¹⁶¹ and social withdrawal¹⁶² have all been highlighted as risk factors in these populations.

Findings from our laboratory studies are consistent with the fact that women generally surpass men in the number of psychiatric problems related to their drug/alcohol use, despite men having significantly higher consumption levels and dependence problems.^{2,145} Moreover, the National Comorbidity Survey found greater prevalence of anxiety, depression, panic disorder, and phobia in female alcohol abusers compared to males,¹⁶³ and almost twice the prevalence

of anxiety disorder has been reported in treatment-seeking CD women compared to men.¹⁶⁴ As such, allostasis of stress-related HPA and SAM systems, increased emotional intensity, and the potential for comorbid affective disorders in drug/alcohol-abusing women may therefore interact as unique risk factors in alcohol- and drug-abusing women.

Similarly, fluctuations in sex hormones across the MC may influence neuroadaptations in stress response and drug craving in several ways—and in so doing have relevant treatment implications. First, the positive effects of cocaine may be potentiated in women during the follicular phase of their cycle to the same levels as men.^{74,106} Although follicular estradiol has been shown to play a lesser role in altering response to stimulants in humans, the equivalent hedonic experience in women compared to men may highlight the follicular phase as a period of increased allostatic susceptibility. Of particular note in this context is that CD females may potentially experience greater emotional intensity in response to HPA arousal,^{131,165} as observed in our laboratory studies.^{60,129}

Second, while increased levels of progesterone and decreased levels of E2/P across the MC in CD women may initially reflect a neuroadaptive response to enhanced, stress-induced HPA and negative affect, the persistence of distress and repeated adaptations may lead to depleted progesterone and allopregnanolone levels.¹⁶⁶ These changes could further predispose women to increased anxiety, negative emotion, and lowered tolerance to stress, which in turn may increase vulnerability to relapse.

Third, the attenuating effects of progesterone suggest that the late luteal (premenstrual) MC phase, which is characterized by endogenous progesterone withdrawal,¹⁶⁷ could represent a phase of increased vulnerability to stress and to cue-related craving. These progesterone-related mechanisms may serve to increase anxiety¹⁶⁸ and insensitivity to the potentiating effects of GABA-modulatory drugs such as alcohol¹⁶⁹ in substance-abusing women. It is notable that in our study we found that E2/P ratios in the late luteal phase of 12 CD women were significantly associated with increased cocaine craving.⁵⁵

In summary, studies reviewed in this article have shown that substance-abusing women may show increased emotional sensitivity to stress-system changes compared to men, alongside sex-specific differences in HPA- and SAM-system responses. Moreover, these unique neuroadaptations in affect and autonomic function may influence relapse vulnerability, comorbid affective disorders, and treatment outcome. Findings also indicate that stress- and reward-system alterations may be mediated by sex hormones or MC phase, suggesting that women may be more susceptible to stress and cue-related craving during the follicular phase, when progesterone levels are low. Such compounded problems may, in turn, highlight the necessity for appropriately tailored, gender-specific treatment programs emphasizing the development of assertiveness training and coping skills for affective disorders, guilt, and low self-esteem.^{160,170}

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TABLE 1
Gender Differences in Stress-System Changes Following Acute Drug Administration

Study	Dose regimen & route	Placebo control	Sample	Gender differences in stress-system changes
Men vs. women				
Netter et al. (1994) ⁶³	0, 0.014, 0.028 mg/kg nicotine (oral)	Y	Healthy volunteers (24 M, 24 F)	M > F: in serum nicotine levels M < F: HR & BP at lower doses
Perkins et al. (1995) ⁶⁴	4 × 20 mg/kg nicotine (nasal spray) 0.5 g/kg alcohol (oral)	Y	Smokers & social drinkers (9 M, 9 F)	M, not F: alcohol decreased vigor & arousal
Kosten et al. (1996) ¹¹	4 studies: about 2 mg/kg cocaine (inhaled)	N	Cocaine dependent (23 M, 11 F)	M = F: plasma cocaine levels, HR, BP M < F: "nervous"
Evans et al. (1999) ⁶⁵	2 x up to six 50 mg doses cocaine across 2 days (smoked)	Y	Cocaine history (11 M, 9 F)	M < F: plasma cocaine levels, HR, BP M > F: "want cocaine"
Singha et al. (2000) ⁶⁶	80 mg/70 kg cocaine (oral)	Y	Cocaine dependent (27 M, 8 F)	M < F: "bad drug effects," "anxious/nervous" M > F: systolic BP
Schuckit et al. (2000) ⁶⁷	0.75 ml/kg (for F); 0.9 ml/kg (for M) alcohol (oral)	Y	FH+ & FH- (alcoholism) (75 M, 38 F)	FH+ males = FH- females: all subjective scales
Gabay et al. (2003) ⁶⁸	10 mg amphetamine (oral)	Y	Healthy volunteers (63 M, 46 F)	M > F: anxiety M = F: all other subscales
Gabay et al. (2005) ⁶⁹	10 mg amphetamine (oral)	Y	FH+ & FH- (alcoholism) (34 M, 38 F)	FH+ males > FH- males: stimulant ratings FH+ females = FH- females
McCance-Katz et al. (2005) ¹²	4 × 1 mg/kg cocaine (inhaled) 1 g/kg & 120 mg/kg alcohol (oral)	Y	Cocaine & alcohol dependent (8 M, 7 F)	M < F: HR following alcohol M < F: "feel good" following cocaine
Acheson et al. (2006) ⁷⁰	0, 7, or 14 mg nicotine (transdermal)	Y	Smokers & social drinkers (22 M, 22 F)	M < F: "positive mood" (after 0 & 7 mg) M > F: "arousal" (after 14 mg)
Vansickel et al. (2007) ⁷¹	0, 2.5, 5, 10, 15 mg amphetamine (oral)	Y	Healthy volunteers (14 M, 13 F)	M > F: "high", "sluggish" M < F: "nausea", diastolic BP
Men vs. women (follicular) vs. women (luteal)				
Lukas et al. (1996) ⁷²	0.9 mg/kg cocaine (inhaled)	Y	Healthy volunteers (7 M, 7 F)	M > F: plasma cocaine levels & detection of cocaine effects M = F: peak HR & subjective measures F (follicular) > F (luteal): "how content do you feel"
Mendelson et al. (1999) ⁷³	0.2, 0.4 mg/kg cocaine (intravenous)	N	Cocaine dependent (12 M, 22 F [11 follicular, 11 luteal])	M = F: plasma cocaine, HR, "feel high" F (follicular) = F (luteal): all cardiovascular & subjective measures
Sofuoglu et al. (1999) ⁷⁴	Study 1: 0.4 mg cocaine (smoked) Study 2: 6 × 0.4 mg cocaine (smoked)	N	Cocaine history (23 M, 21 F) Cocaine history (11M, 12 F)	M & F (follicular) > F (luteal): "feel high" M < F: "feel high," HR, heart racing
White et al. (2002) ⁷⁵	15 mg amphetamine (oral)	Y	Healthy volunteers (7 M, 13 F)	F (follicular) > F (luteal): "feel high," "feel drug," "want more" M > F (luteal): "feel drug," "want more"

Study	Dose regimen & route	Placebo control	Sample	Gender differences in stress-system changes
Collins et al. (2007) ⁷⁶	0.06, 0.34, 0.69, 1.37 mg/kg cocaine (inhaled)	N	Cocaine dependent (10 M, 8 F)	M = F: all subjective & cardiovascular measures F (follicular) = F (luteal): all subjective & cardiovascular measures
Women only, follicular vs. luteal				
Justice & de Wit (1999) ⁷⁷	15 mg amphetamine (oral)	Y	Healthy volunteers (16 F)	F (follicular) > F (luteal): “high,” “energetic,” “intellectually efficient,” “euphoric,” “like/want drug”
Evans et al. (2002) ⁷⁸	0, 6, 12, or 25 mg cocaine (smoked)	Y	Cocaine history (11 F)	F (follicular) > F (luteal): HR, “good drug effect,” “high,” “stimulated,” dysphoric mood
Kouri et al. (2002) ⁷⁹	0.9 mg/kg cocaine (inhaled)	Y	Healthy volunteers (7 F)	F (follicular) = F (luteal): all subjective measures
Women only, early follicular vs. late follicular				
Justice & de Wit (2000) ⁸⁰	15 mg amphetamine (oral)	Y	Healthy volunteers (19 F)	F (late follicular) > F (early follicular): “unpleasant stimulation” F (late follicular) < F (early follicular): “unpleasant sedation”
Exogenous sex hormone administration: women only, early follicular				
Justice & de Wit (2000) ⁸¹	10 mg amphetamine (oral) plus either 0.8 mg estrogen or placebo (patch)	Y	Healthy volunteers (11 estrogen, 9 placebo)	Estrogen > placebo: “pleasant stimulation” Estrogen < placebo: “want more”
Sofuoglu et al. (2002) ⁸²	3 × 4 mg cocaine (smoked) 200 mg progesterone (oral)	Y	Cocaine dependent (5 F)	Progesterone < placebo: “feel the effect of last dose”
Lile et al. (2007) ⁸³	0, 3.125, 7.5, 15 mg/70 kg amphetamine (oral) 0.25 mg estrogen (oral)	Y	Healthy volunteers (10 F)	Estrogen > placebo: “like drug” & stimulant subscale
Exogenous sex hormone administration: men vs. women				
Sofuoglu et al. (2004) ⁸⁴	0.3 mg/kg cocaine (inhaled) 200 mg progesterone (oral)	Y	Cocaine dependent (6 M, 4 F [follicular])	Progesterone < placebo: diastolic BP, “high,” “feel the effect of last dose”
Evans & Foltin (2006) ⁸⁵	6 × 0, 6, 12, or 25 mg cocaine (smoked) 150 mg progesterone (oral)	Y	Cocaine history (10 M, 11 F)	F (follicular & progesterone) < F (luteal): “good drug effect” cluster scores, “drug quality” cluster scores, “willing to pay”

BP, blood pressure; F, female; FH, family history (+ or –); HR, heart rate; M, male.

TABLE 2

Gender Differences in Stress-System Changes Following Stress or Drug Cue

Study	Stressor/cue	Sample	Gender differences in stress-system response
Frankenhaeuser et al. (1976) ¹⁰⁹	Stroop & repeated venipuncture	Healthy volunteers (6 M, 6F)	F < M: epinephrine
Frankenhaeuser et al. (1978) ¹¹⁰	Examination stress	Healthy volunteers (19 M, 30 F)	F < M: epinephrine, MHPG, "success & confidence" F < M: "discomfort & failure"
Collins & Frankenhaeuser (1978) ¹¹¹	Stroop	Healthy volunteers (6 M, 6 F)	F < M: HR in control condition F < M: epinephrine, plasma cortisol, HR
Jorgensen & Houstén (1981) ¹¹²	Stroop, mental arithmetic (serial 7s), shock avoidance	FH+ (hypertension) (14 M, 16 F) FH- (hypertension) (13 M, 15 F)	F FH+ > F FH-: systolic BP M FH+ = M FH-: systolic BP
Hastrup & Light (1984) ¹¹³	Unsignaled shock-avoidance reaction time and cold pressor task	Healthy volunteers (12 M, 24 F [follicular & luteal])	F (follicular) < F (luteal) & M: HR & BP on shock test only
Frankenhaeuser et al. (1986) ¹¹⁴	Examination stress	Healthy volunteers	F < M HMPG
Tersman et al. (1991) ¹¹⁵	Mental arithmetic and cold pressor task	Healthy volunteers (15 M, 15 F [luteal & follicular])	F < M: systolic BP F > M: HR in mental arithmetic F (luteal) > F (follicular): glucocorticoid response after cold pressor task
Kirschbaum et al. (1992) ¹¹⁶	Trier Social Stress Test, CRH challenge; physical exercise	Study 1: Healthy volunteers (19 M, 13 F) Study 2: Healthy volunteers (23 M, 14 F) Study 3: Healthy volunteers (22 M, 26 F)	F < M: ACTH, plasma cortisol following Trier Social Stress Test F = M: ACTH, plasma cortisol, CRH, & physical exercise
Allen et al. (1993) ¹¹⁷	Math task, mirror tracing, Stroop, isometric handgrip	Healthy volunteers (22 M, 22 F)	F < M: systolic BP, diastolic BP F > M: HR
Rubonis et al. (1994) ⁹⁸	Beverage cue followed by mood induction	Alcohol dependent (38 M, 19 F)	F > M: "urge reactivity" following negative mood
Kirschbaum et al. (1995) ¹¹⁸	Trier Social Stress Test	Healthy volunteers (19 M, 29 F)	F < M: plasma cortisol
Kudielka et al. (1998) ¹¹⁹	Trier Social Stress Test	Healthy volunteers (postmen) (34 M, 36 F)	F < M: ACTH, plasma cortisol, salivary cortisol
Sinha et al. (1998) ¹²⁰	0.85 g/kg ethanol followed by public speech	Social drinkers (61 M, 54 F)	
Willner et al. (1998) ⁹⁶	25 ml low-alcohol beer, followed by musical depression induction	Social drinker (72 M, 72 F)	F < M: "craving" following alcohol consumption F < M: liking for alcohol reinforcers after negative mood
Kirschbaum et al. (1999) ¹²¹	Trier Social Stress test & 0.25 mg & ACTH 1–24 challenge	Healthy volunteers (20 M, 19 F [follicular], 20 F [luteal], 21F [taking oral contraceptive])	Trier Social Stress Test F < M: ACTH M = F (follicular) > F (luteal) = F (taking oral contraceptive): salivary cortisol ACTH challenge F (luteal) > M > F (follicular) > F (taking oral contraceptive): salivary cortisol
Earle et al. (1999) ¹²²	Harassment	Healthy volunteers (28 M, 32 F)	F < M: plasma cortisol, diastolic BP F > M: HR, "hostility"
Matthews et al. (2001) ¹²³	Mental arithmetic & public speaking	Healthy volunteers (31 M, 31 F)	F < M: diastolic BP F < M: systolic BP, diastolic BP, epinephrine during recovery

Study	Stressor/cue	Sample	Gender differences in stress-system response
Seeman et al. (2001) 124	30-minute cognitive challenge	Healthy volunteers (9 M, 17 F [younger]; 7 M, 7 F [older])	F < M: salivary cortisol in younger adults F > M: salivary cortisol in older adults
Stroud et al. (2002) 125	Achievement stress (math & verbal) & rejection stress (social interaction)	Healthy volunteers (24 M, 26 F)	F < M: salivary cortisol following achievement stress F > M: salivary cortisol following rejection stress
Traustadottir et al. (2003) ¹²⁶	Matt Stress Test Reactivity Protocol, Stroop, cold pressor task, interpersonal stressor, anagram test, mental arithmetic	Healthy volunteers (8M, 8 F) (55–75 years old)	F < M: plasma cortisol, diastolic BP F = M: HR, systolic BP, ACTH
Zimmer et al. (2003) 127	Pain (cold pressor task modified)	Healthy volunteers (39 M, 37 F)	F < M: salivary cortisol F = M: "pain intensity," "unpleasantness"
Kudielka et al. (2004) 128	Trier Social Stress Test	Healthy volunteers (28 children; 34 young adults; 26 older adults)	F < M: HR in children and young adults F = M: HR in older adults
Back et al. (2005) ¹⁶	Cold pressor task & mental arithmetic task	Cocaine dependent (18 M, 21 F)	F > M: "stress," "nervousness," "pain" F < M: skin conductance, HR
Brady et al. (2006) ³³	Cold pressor task	Alcohol dependent (19 M, 15 F) PTSD (12 M, 18 F) Alcohol dependent & PTSD (16 M, 12F)	F < M ACTH, w/greater ACTH blunting in alcohol-dependent Fs
Fox et al. (2006) ¹²⁹	Personalized stress and cue imagery	Cocaine dependent (25 M, 25 F)	F < M: basal systolic BP, plasma cortisol, ACTH F < M: systolic BP, plasma cortisol, ACTH in response to stress & cue F > M: basal HR, prolactin
Nesic & Duka (2006) 97	Public speech followed by alcohol cue	Heavy social drinkers (16 M, 16 F)	F < M: alcohol consumption Stressed F < nonstressed F: skin conductance
Fox et al. (2007) ⁶⁰	Personalized stress and cue imagery	Alcohol dependent (21 M, 21 F) Social drinkers (21 M, 21 F)	Alcohol-dependent F > alcohol-dependent M, social-drinking F, social-drinking M: "sadness," "anxiety," "anger," "fear," "behavioral arousal"
Back et al. (2008) ¹³⁰	Trier Social Stress Test & CRH challenge	Healthy volunteers (21 M, 25 F)	F < M: basal ACTH & BP F > M: ACTH & BP response F smokers < F nonsmokers: plasma cortisol
Chaplin et al. (2008) 131	Personalized stress and cue imagery	Social drinkers (27 M, 27 F)	F > M: "sadness" & "anxiety" following stress M > F: diastolic BP following stress

BP, blood pressure; F, female; FH, family history (+ or -); HR, heart rate; M, male; MHPG, 3-methoxy-4-hydroxy-phenylethylene glycol; PTSD, posttraumatic stress disorder.